IN THE UNITED STATES PATENT

AND TRADEMARK OFFICE

Applicant(s): Kazuhiro FUKUNAGA et al

Serial No.: 10/509,839

Filed: April 1, 2003

For: viscous preparation for DENTAL USE CONTAINING BASIC FIBROBLAST GROWTH FACTOR

Art Unit: 1617

Examiner: Abigail M. Cotton

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

SIR:

I. Mr. Moriyuki Ohkuma, a citizen of Japan and having an address of 1-15-27-3, Takayanagi, Fujieda, Shizuoka, Japan, who declare and say as follows.

I finished from Faculty of Engineering, Department of Industrial Chemistry of Kogakuin University in 1979,

I was awarded the degree of Doctor of Pharmacy from Meijo University in 2000,

I have been employed by Kaken Pharmaceutical Co., Ltd. in April, 1974, and engaged in research and development on drug formulation as of today,

I am presently in charge of Drug Formulation Department at the Central Research Laboratories of the company; and

I understand the English language. I studied the Final

Rejection dated May 10, 2007 received in the above-identified application.

In order to show that the present invention is not obvious over the references cited by the Examiner, I have conducted comparative experiments as mentioned below under my supervision.

II. Comparative experiments

In order to show excellent effect (stability) of using hydroxypropylcellulose as a thickener in combination with basic fibroblast growth factor (bFGF), the following experiments are carried out at 25°C for one week.

1. Experimental materials

In the experiment, the following materials were used.

(1) bFGF (Trafermin (genetical recombination)) (available from Scios Inc., U.S.A., Lot No.: PI80829)
(2) Cellulose derivatives

Name	Trade name	Regulation	Manufacturer	Lot No.
HPC	HPC-H	Japanese Pharmacopoeia (Hydroxypropoxy group: 65.9%)	Nippon Soda Co., Ltd., Japan	NFK-1101
MC	METOLOSE SM-1500	Japanese Pharmacopoeia	Shin-Etsu Chemical Co., Ltd., Japan	706854
HPMC	METOLOSE 60SH-4000	Japanese Pharmacopoeia	Shin-Etsu Chemical Co., Ltd., Japan	7Y162

Note: HPC; Hydroxypropyl cellulose
MC; Methylcellulose mentioned in Finkenaur
HPMC; Hydroxypropylmethylcellulose mentioned in Finkenaur

2. Experimental method

(1) Preparation of viscous solution

With regard to the respective cellulose derivatives, each 6% by weight aqueous solution was prepared by dissolving in water.

(2) Preparation of aqueous bFGF solution

According to the concentration of raw bFGF solution, it was diluted with water to prepare an aqueous bFGF solution with a concentration of 8 mg/mL.

(3) Preparation of viscous preparation (prepared twice)

Each viscous solution (6% by weight)of the respective cellulose derivatives was mixed with the aqueous bFGF solution (8 mg/mL) in a volume ratio of 1:1 to prepare respective viscous preparations (bFGF concentration: 4 mg/mL, Cellulose derivative concentration: 3% by weight).

(4) Preparation of control solution (prepared twice)

The aqueous bFGF solution (8 mg/mL) was mixed with water in a volume ratio of 1:1 to prepare a control solution (bFGF concentration: 4 mg/mL).

3. Analysis method (Stability test)

With regard to the respective viscous preparations, stability test was carried out under the following conditions.

(1) Preservation temperature: 25°C±2°C (dark place)
(2) Preserved term: 1, 2, 3, 5 and 7 days
(3) A purity of bFGF of the respective viscous preparations after preservation was measured by reverse phase HPLC (High performance liquid chromatography).

4. Evaluation standard

A purity of bFGF at the time of starting the experiment of the control solution was made 100%, and a remaining ratio of the bFGF in the respective test solutions after preservation was compared with the initial amount. A sample in which an amount of the bFGF is substantially not changed as compared with the initiation of the experiment is judged to have good stability.

5. Results

The results are as shown in the following Table 1 and Fig. 1.

Table 1 bFGF Remaining ratio (%)
in respective viscous preparations at 25°C

Sample	Preserved term (Days)					
	Initial	1	2	3	5	7
HPC viscous preparation	99.6	98.0	96.6	95.8	95.1	94.9
MC viscous preparation	98.8	95.5	92.9	91.8	89.9	87.6
HPMC viscous preparation	98.6	94.9	91.9	90.1	88.3	85.5

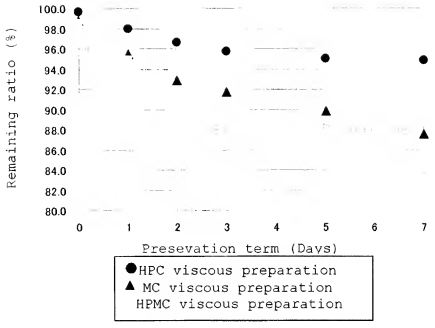

Fig.1 bFGF remaining ratio in respective viscous preparations at 25°C

Incidentally, as a reference, test results of the experimental data shown in the present specification (mentioned on page 14, Table 1) and those shown in the previously submitted Declaration under 37 CFR 1.132 are shown in Tables 2 and 3 below.

Table 2 (mentioned on page 14, Table 1)

HPC Preparation	Preservation time (hr)		
	8	24	42
Preparation 1a (0.89mg/mL)	98.7	98.1	99.1
Preparation 1b (2.67mg/mL)	98.6	99.6	98.9

Table 3 (experimental results mentioned in the previously submitted Declaration)

Sample	Preservation time (hr)	
	Initial	24
HPC	99.5	98.2
MC	98.0	90.4
HPMC	98.7	93.2

6. Consideration

As can be seen from the results shown in the above Tables and Fig. 1, it can be understood that whereas all the viscous preparations were gradually reduced in their remaining ratios of bFGF with a lapse of time, only hydroxypropylcellulose showed good stability of the bFGF remaining ratio as 95% after preservation at 25°C for 7 days.

On the other hand, when bFGF is used in combination of the other cellulose derivatives such as methylcellulose and hydroxypropylmethylcellulose which is mentioned as a preferred one in Finkenaur, the remaining ratio of the bFGF after the preservation at 25°C for 7 days were both less than 88%. This means that the cellulose derivative other than hydroxypropyl-cellulose of the present invention cannot be practically used.

That is, a standard content of a medicament is generally determined in the range of "95 to 105%", so that if the remaining ratio of bFGF is 88% or less, it is far from the standard content. In addition, more than 5% change from the initial content in the drug product stabilization test is defined as "significant change in quality" ("significant change" in ICH Guideline Q1A 2.2.7.1). In the comparative preparations of using MC or HPMC mentioned in the above Table

3, the remaining ratios were decreased up to about 10% of bFGF which comply with the "significant change in quality" so that they cannot be practically used.

III. Conclusion

I believe that the above results would indeed be surprising and could never be expected from the description of the cited references. Thus, I do not believe that the present invention is obvious over the references cited by the Examiner.

IV. I further declare that all statements made herein of may own knowledge are true and that all statements made in information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: October 31, 2007

Moriyuki Ohkuma

Moriyuki Ohkuma